Archival Report

Biological Psychiatry: Celebrating 50 Years

Probing Brain Developmental Patterns of Myelination and Associations With Psychopathology in Youths Using Gray/White Matter Contrast

Linn B. Norbom, Nhat Trung Doan, Dag Alnæs, Tobias Kaufmann, Torgeir Moberget, Jaroslav Rokicki, Ole A. Andreassen, Lars T. Westlye, and Christian K. Tamnes

ABSTRACT

BACKGROUND: Cerebral myeloarchitecture shows substantial development across childhood and adolescence, and aberrations in these trajectories are relevant for a range of mental disorders. Differential myelination between intracortical and subjacent white matter can be approximated using signal intensities in T1-weighted magnetic resonance imaging.

METHODS: To test the sensitivity of gray/white matter contrast (GWC) to age and individual differences in psychopathology and general cognitive ability in youths (8–23 years), we formed data-driven psychopathology and cognitive components using a large population-based sample, the Philadelphia Neurodevelopmental Cohort (N = 6487, 52% female). We then tested for associations with regional GWC defined by an independent component analysis in a subsample with available magnetic resonance imaging data (n = 1467, 53% female).

RESULTS: The analyses revealed a global GWC component, which showed an age-related decrease from late childhood and across adolescence. In addition, we found regional anatomically meaningful components with differential age associations explaining variance beyond the global component. When accounting for age and sex, both higher symptom levels of anxiety or prodromal psychosis and lower cognitive ability were associated with higher GWC in insula and cingulate cortices and with lower GWC in pre- and postcentral cortices. We also found several additional regional associations with anxiety, prodromal psychosis, and cognitive ability.

CONCLUSIONS: Independent modes of GWC variation are sensitive to global and regional brain developmental processes, possibly related to differences between intracortical and subjacent white matter myelination, and individual differences in regional GWC are associated with both mental health and general cognitive functioning.

Keywords: Adolescence, Brain development, Mental health, MRI, Myelination, Signal intensity

https://doi.org/10.1016/j.biopsych.2018.09.027

Adolescence is a time of extensive changes in the sociocultural domain, as well as within the body, cognition, emotion, and behavior (1,2). Brain development during this period involves multiple biological processes that dynamically interact with the environment and shows temporal and spatial heterogeneity across tissue types, measures, and individuals (3–6). Increased knowledge about these brain developmental patterns and their individual differences is key to informing ontogenetic models of psychopathology.

Although current psychiatric diagnostic tools rely on manifest symptoms that often appear relatively late in illness progression, numerous mental disorders are considered to have a neurodevelopmental origin (7,8), with additional risk factors related to social behavior and adverse effects of drug and alcohol use (9). Moreover, common symptoms of mental illness form spectra in the general population (10–13). Neuroimaging studies using population-based youth samples may thus provide early identification of individuals at risk and insight into the development of mental disorders and may discern brain phenotypes associated with the full range of variation in symptoms of mental illness.

The information processing analogy of the brain has provided a useful framework for the study of brain aberrations in clinical populations (14). An underlying assumption is that a healthy brain is characterized by efficient communication between regions, made possible by a structural backbone of myelinated axons and pathways. Myelin is key for efficient neural signaling as it increases speed and reliability of the nerve signal, provides support, and prevents aberrant sprouting of nerve connections (15,16). Neuroimaging studies have described developmental trajectories (3,17) and case-control differences (18) in the organization and microstructure of

© 2018 Society of Biological Psychiatry.

ISSN: 0006-3223

these white matter (WM) pathways. A recent finding in an overlapping sample, indicate that frontotemporal WM dysconnectivity is a transdiagnostic brain phenotype, associated with both higher levels of psychopathology and lower cognitive abilities (19).

Importantly, beyond WM, the cerebral cortex is also myelinated. Intracortical myelin is predominantly found in deeper layers of cortex, in part due to proliferation of myelin from WM, penetrating the inner periphery of cortical neuropil (20–22). Intracortical myelination is a crucial feature of brain development (23), of which maturational timing conforms with a general posterior-anterior gradient, with additional regional specificity as highly myelinated regions, such as sensorimotor and early association cortices, mature early (23,24). Cortical myelin content, as indirectly assessed in vivo using magnetic resonance imaging (MRI), has been linked to cognitive performance in youths (25) and adults (26), and abnormal intracortical myelination is a candidate mechanism for common mental disorders (8,16,27,28). Compared with closely related nonhuman primates, postnatal intracortical myelination in humans is exceptionally extended (29). Although there are clear benefits to allow for prolonged environmental influences on brain circuit establishment and refinement, this human-specific shift in timing and extension of cortical development may come at a cost, as diverse forms of psychopathology typically emerge during adolescence (30).

Cholesterol in myelin is a major determinant of the intensity in the T1-weighted MRI signal (31,32), and cortical gray matter (GM) intensity has been shown to correspond closely with histologically based myelin profiles (33), specifically with myelin rather than iron content (34). The differential myelination of the cerebral cortex and subjacent WM can be approximated using the gray/white matter contrast (GWC) of the T1-signal intensity. Lower GWC indicates that GM and WM intensities are more similar, while a higher contrast reflects a larger discrepancy; however, the biological interpretation is likely complex. GWC exhibits significant heritability (35) and shows regional aging-related patterns (36). Although dysmyelination is a viable candidate mechanism for brain network dysfunction, few studies have examined this measure in relation to mental health, and those that have did so only in adults with psychosis (37–39).

The present study aimed to test the sensitivity of GWC to individual differences in age and psychopathology in youths (8–23 years). We used the Philadelphia Neurodevelopmental Cohort ([PNC], N = 6487) to develop data-driven clinical and cognitive components (19). In a subsample with available MRI data (n = 1467), we performed an independent component analysis (ICA) of vertexwise GWC across the brain surface and tested for associations with age, different psychopathology components, and general cognitive ability. We hypothesized that GWC generally would show a negative association with age, possibly owing to protracted myelination of cortex compared with subjacent WM, as well as regional age-related patterns. Next, we hypothesized that youths with increased symptoms of psychopathology or lower cognitive ability would show regionally higher GWC, possibly indicating lower levels of intracortical myelin compared with subjacent WM.

METHODS AND MATERIALS

Participants

The analyses were based on the publicly available PNC (Permission No. 8642), a large population-based sample comprising MRI, cognitive, clinical, and genetic data (40,41). Further details on the project and procedures are described in the Supplement and elsewhere (40,42,43).

As reported previously (19), all individuals (N = 6487, 3379 female) age 8 to 22 years who were made available from the PNC were included for psychopathology and cognitive analyses. Missing clinical item scores were replaced with the nearest neighbor value based on Euclidean distance. We then formed data-driven cognitive and clinical components and tested for associations with GWC in a subsample of individuals with available and quality-controlled MRI data. From 1601 available scans, we excluded participants with severe medical health conditions (n = 70), based on a severity index rating by trained personnel in the PNC study team (44), or owing to incomplete or poor-quality MRI data (n = 64, see MRI Acquisition and Processing). The final MRI sample consisted of 1467 individuals (776 female) age 8.2 to 23.2 years. Respectively, 66 and 65 participants had missing clinical and cognitive data and were excluded from relevant analyses. See Supplemental Table S1 for MRI- and psychopathology/cognitive sample demographics.

Clinical Assessment and Data-Driven Decomposition of Psychopathology

The clinical assessment consisted of a computerized and modified version of the neuropsychiatric interview Kiddie-Schedule for Affective Disorders and Schizophrenia. This interview assesses psychological treatment history and lifetime occurrence of psychopathology. For participants age 11 to 17 years, information from collaterals were included, while this was the only source for 8- to 10-year-old participants (40). Attempting to separate domains and uncover the empirical correlation structure of psychopathology across diagnostic boundaries, using the larger set of participants (N = 6487), we submitted 129 clinical symptom score items, covering 18 clinical domains, to ICA using Icasso (http://research.ics.aalto.fi/ica/icasso/) (45), as reported previously (19). The analysis yielded seven psychopathology components. In addition, as a general measure of psychopathology, we computed the mean subject weight across these components.

Cognitive Assessment and Definition of a General Cognitive Factor

Participants completed a computerized test battery evaluating a range of cognitive domains (43). Retrieving a single factor to estimate general cognitive ability, conceptually similar to the IQ score, we included performance scores from 17 diverse tests in a principal component analysis without rotation in the larger set of participants (N = 6487) as reported previously (19). Owing to high correlations between test scores and age, all raw scores were age residualized by linear regression and standardized before running the principal component analysis. The first factor was extracted as a general measure of cognitive function (gF), explaining 12% of the variance.

MRI Acquisition and Processing

MRI scans were acquired on a single 3T Siemens TIM Trio whole-body scanner (Siemens, Erlangen, Germany) without any software or hardware upgrades (40) (see Supplemental Methods). We used FreeSurfer 5.3 (http://surfer.nmr.mgh.harvard.edu) for cortical reconstruction and volumetric segmentation (46–49). To assess the quality of the cortical reconstructions, we implemented a flagging procedure based on robust principal component analysis for detecting signal-to-noise and segmentation outliers (50,51). We carefully inspected flagged datasets, and minor edits were performed when necessary (n = 459). Scans from 63 participants were excluded owing to poor image quality and poor Euler number (52) (see Supplemental Table S2).

Based on previous implementations (37,53,54), for each participant, we sampled signal intensities from the nonuniform intensity normalized volume (nu.mgz) using the FreeSurfer function mri_vol2surf. For each vertex, GM intensities were sampled at six equally spaced points, starting from the gray/white boundary and ending 60% into cortical GM. We selected this end point to minimize contamination of voxels containing cerebrospinal fluid. WM intensities were sampled at each vertex at 10 equally spaced points, starting from the gray/white boundary and ending at a fixed distance of 1.5 mm into subcortical WM. To obtain single separate measures of GM and WM intensity per vertex, we calculated the average intensity value for each tissue type. GWC was then computed as $100 \times (\text{white} - \text{gray})/[(\text{white} + \text{gray})/2]$ (37), such that a higher value reflects greater difference between GM and WM signal intensities. The GWC surface maps were smoothed using a Gaussian kernel of 10-mm full width at half maximum.

We then performed ICA to decompose the GWC surfaces into spatially independent modes of variations using Icasso (45). We used a model order of 15, pragmatically chosen based on a compromise between data reduction and total explained variance.

See Supplemental Methods for processing procedures for comparison between GWC and the complementary method of T1-T2 ratio.

Statistical Analyses

We first tested the associations between each GWC independent component (IC) and age by computing the t statistics of the linear and quadratic age effects on each GWC IC using general linear models (GLMs), covarying for sex, and p values were corrected using the false discovery rate procedure with a significance threshold of .05 (55). To visualize the observed effects, we used locally estimated scatterplot smoothing (loess) and ggplot2 (56) in R (https://www.r-project.org/). We also used loess to assess WM and GM separately (see Supplemental Methods).

Second, we tested for associations between the psychopathology component loadings and gF and GWC ICs using GLMs with age and sex as covariates. We also report associations with the quadratic age term when significant. For each of the 15 GWC ICs, we ran GLMs where one of the seven psychopathology ICs, mean psychopathology score, or gF was included as an independent variable, resulting in 135 (15×9) models. The p values obtained from all models were then corrected using the false discovery rate procedure with a significance threshold of .05 (55). For follow-up analyses concerning brain size and ethnicity, see Supplemental Methods. To investigate possible interactions between age and psychopathology and gF on GWC ICs, we repeated the above models including an additional interaction term between these variables. To assess the dynamics of effects not necessarily well modeled by GLM, we also performed a sliding window analysis and a subgroup visualization (see Supplemental Methods).

Third, to allow for comparison with a more conventional vertexwise approach, we examined the vertexwise effects of age, covarying for sex, and for psychopathology and gF, covarying for sex and age, on GWC, using GLM as implemented in the Permutation Analysis of Linear Models toolbox (57). To assess statistical significance we used 10,000 permutations and familywise error correction with threshold-free cluster enhancement (58) and a significance threshold of $p < .05$, corrected. For follow-up analyses where thickness was added as a vertexwise covariate, see Supplemental Methods.

RESULTS

ICA Decomposition of GWC

Figure 1 shows the 15 GWC components from Icasso (45). In total, these components explained 29% of the total variance. With some notable exceptions, the maps were highly bilateral and symmetrical and were region specific, except for a single global component. Regional specification corresponded well with regions separated within T1-T2 ratio maps and histological profiles, concerning both myelin content and developmental patterns (23,24,33).

Associations Between GWC and Age

The global GWC component showed a marked negative linear age association ($t = -14.68$, $p = 1.27 \times 10^{-45}$). Importantly, all remaining GWC ICs must be understood as reflecting independent variance beyond this global component. Components reflecting pre- and postcentral cortices showed strong linear negative age-associations ($t = -24.34$, $p = 3.70 \times 10^{-110}$ and $t = -21.37$, $p = 1.92 \times 10^{-88}$, respectively), and the occipital component also showed a highly significant negative association ($t = -8.8$, $p = 3.83 \times 10^{-18}$). The remaining ICs showed either slight or marked linear positive age associations with t values ranging from 6.49 to 24.91 (all $p < .05$). The superior parietal and left lateral anterior components did not show a significant linear age effect. Loess visualization of the associations between GWC ICs and age are shown in Figure 1. See Supplemental Results and Supplemental Figure S1 for loess visualization of GM and WM separately.

Associations Between GWC and Psychopathology and gF

Figure 2 shows the results from the GLMs testing for associations between GWC and clinical and cognitive scores. There were several significant associations between GWC and anxiety (IC2) and prodromal psychosis (IC4). Specifically, higher loading on either anxiety or prodromal psychosis was associated with higher GWC in left lateral posterior cortex ($t = 3.01$, $p = 1.78 \times 10^{-2}$ and $t = 2.85$, $p = 2.60 \times 10^{-2}$, respectively)

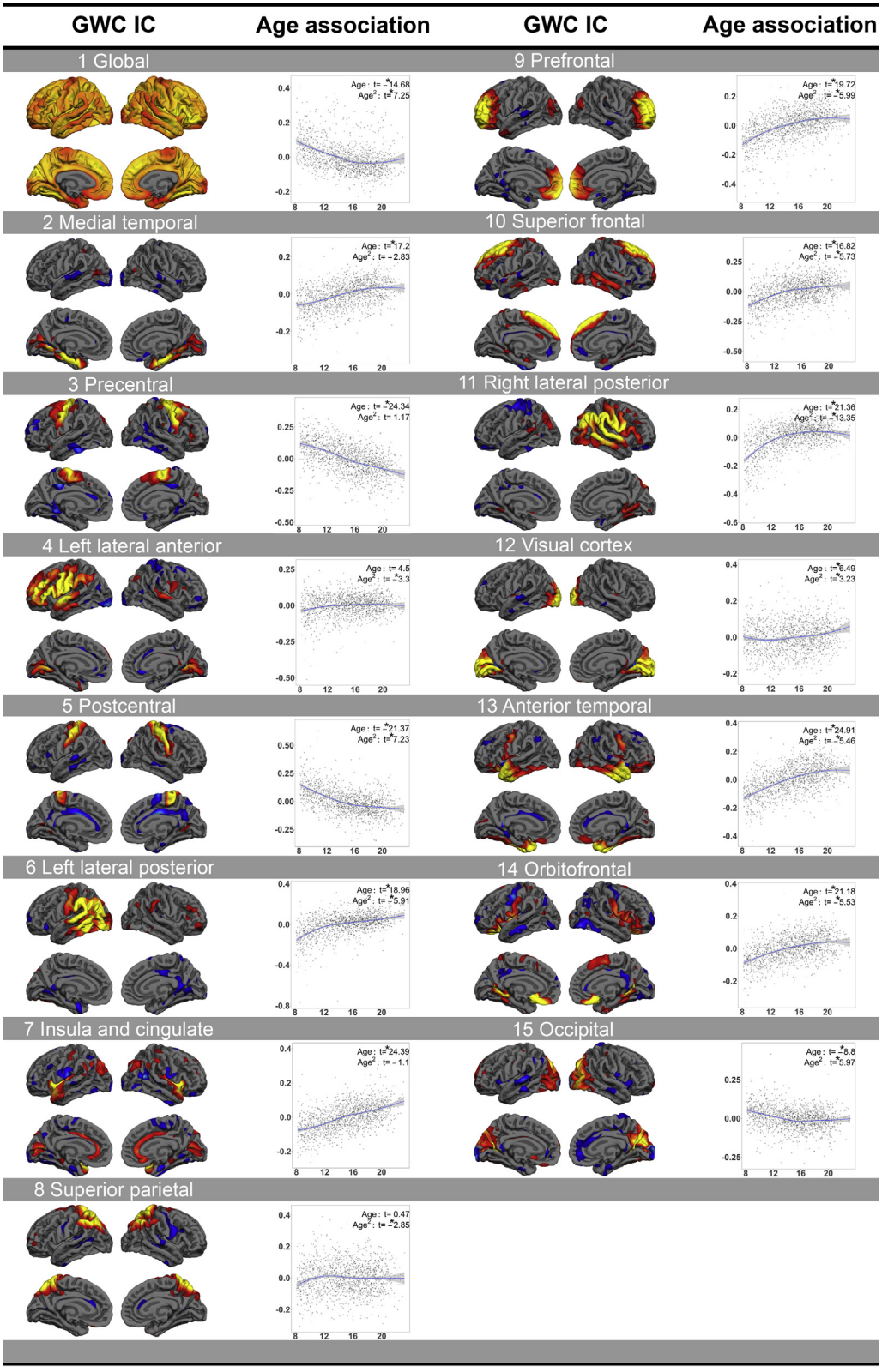

Figure 1. Gray/white matter contrast (GWC) independent components (ICs) and their associations with age. The GWC IC columns show the number, name, and anatomical representation. For the GWC IC maps, thresholds were set at 1 to 3 SDs, except "1 Global," which is set at 1 to 9 SDs. The age association columns show loess visualizations of the age associations. The *t* statistics for age and age^2, covarying for sex, are shown in the top right corners. *False discovery rate corrected $p \leq .05$.

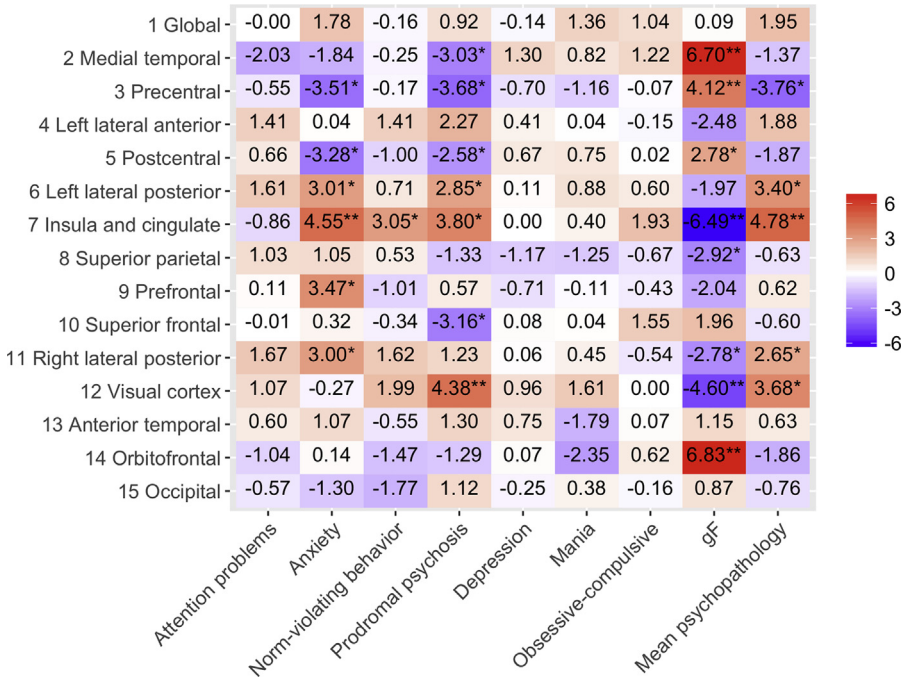

Figure 2. The *t* statistics of the associations between gray/white matter contrast and psychopathology. The y-axis shows each gray/white matter contrast independent component. The x-axis shows each psychopathology independent component, general measure of cognitive function (gF), and mean psychopathology score. The map is color scaled so that red squares show positive associations, while blue squares show negative associations, covarying for age, age^2 when significant, and sex. *Corrected $p \leq .05$; **corrected $p \leq .01$.

and insula and cingulate cortices ($t = 4.55$, $p = 1.33 \times 10^{-4}$ and $t = 3.8$, $p = 2.28 \times 10^{-3}$, respectively), and with lower contrast in precentral ($t = -3.51$, $p = 4.86 \times 10^{-3}$ and $t = 3.68$, $p = 2.75 \times 10^{-3}$, respectively) and postcentral ($t = -3.28$, $p = 8.91 \times 10^{-3}$ and $t = -2.58$, $p = 4.96 \times 10^{-2}$, respectively) cortices. Anxiety showed additional positive associations in prefrontal ($t = 3.47$, $p = 5.27 \times 10^{-3}$) and right lateral posterior ($t = 3.00$, $p = 1.78 \times 10^{-2}$) cortices. Prodromal psychosis showed an additional positive association in the visual cortex ($t = 4.38$, $p = 2.45 \times 10^{-4}$) and additional negative associations in medial temporal ($t = -3.03$, $p = 1.78 \times 10^{-2}$) and superior frontal ($t = -3.16$, $p = 1.29 \times 10^{-2}$) cortices.

Except for a single positive association between norm-violating behavior and GWC in insula and cingulate cortices ($t = 3.05$, $p = 1.76 \times 10^{-2}$), we found no significant associations between the other psychopathology components and GWC. There were, however, significant associations between mean psychopathology score and several GWC components, but these overlapped with the effects of anxiety and/or prodromal psychosis.

General cognitive ability, as indexed by gF, was positively associated with GWC in medial temporal ($t = 6.70$, $p = 2.09 \times 10^{-9}$), precentral ($t = 4.12$, $p = 6.7 \times 10^{-4}$) and postcentral ($t = 2.78$, $p = 3.07 \times 10^{-2}$), and orbitofrontal ($t = 6.83$, $p = 1.76 \times 10^{-9}$) cortices, and it was negatively associated with GWC in insula and cingulate ($t = -6.49$, $p = 5.48 \times 10^{-9}$), superior parietal cortex ($t = -2.92$, $p = 2.19 \times 10^{-2}$), right lateral posterior cortex ($t = -2.77$, $p = 3.07 \times 10^{-2}$), and visual cortex ($t = -4.60$, $p = 1.25 \times 10^{-4}$). Six of these eight associations between general cognitive ability and GWC spatially overlapped with associations between psychopathology and GWC, but with effects in the opposite direction. The correlation with gF loading was −0.14 and −0.13 for anxiety and prodromal psychosis loading, respectively. See Supplemental Results for brain size added as a covariate (Supplemental Figure S2) and for analyses within the two largest ethnicity groups (Supplemental Figure S3). Briefly, adding brain size expectedly reduced effect sizes somewhat, but association patterns were retained. Contrarily, performing separate analyses within Caucasians and African Americans/blacks indicated differential association patterns.

We found no significant interactions between age and psychopathology or gF on the GWC ICs. For GLMs with interaction terms, sliding window results, and loess subgroup visualization, see Supplemental Figures S4–S6.

Vertexwise Associations Between GWC and Age, Psychopathology, and gF

Figure 3 shows the results from the vertexwise analyses. Briefly, permutation testing revealed a near global negative association between age and GWC, indicating lower GWC in widespread regions with higher age. Strongest negative associations were seen in regions around the central sulcus (Supplemental Table S3). These results generally correspond well with the results from the ICA approach. For results where thickness was added as a vertexwise covariate, see Supplemental Results and Supplemental Figure S7. Additionally, for per-vertex full and partial correlations controlling for age between thickness and GWC, see Supplemental Figures S8 and S9. In short, adding thickness had minor effects on results, and correlations between GWC and thickness were generally low. For results on the vertexwise associations among psychopathology and gF and GWC, see Supplemental Results. Briefly, there were no significant associations of the psychopathology components, but there were negative

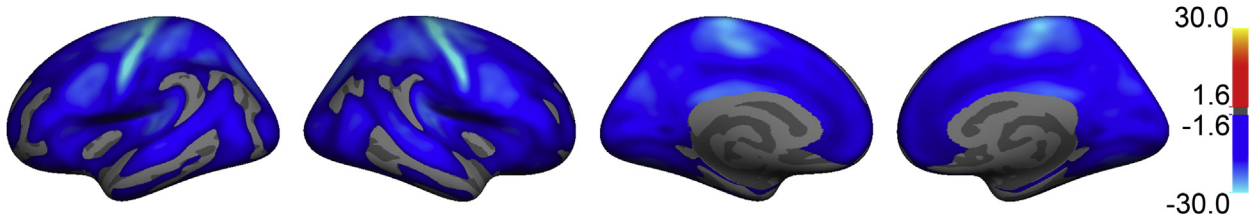

Figure 3. Vertexwise associations between age and gray/white matter contrast. The *t* statistics are masked by familywise error corrected *p* values with a threshold set at a minimum $-\log_p$ of 1.6 to correct for two hemispheres. Blue regions represent negative age associations.

significant associations with gF and GWC (Supplemental Figure S10).

Comparison Between GWC Map and T1-T2 Ratio Map

Figure 4 depicts the mean GWC surface map from all participants compared with the Conte69 (http://brainvis.wustl.edu/wiki/index.php//Caret:Atlases/Conte69_Atlas) mean T1-T2 ratio map provided by Human Connectome Project (see Supplemental Results for detailed descriptions). For mean GM and WM surfaces displaying intensity spread across the cerebrum, refer to Supplemental Figure S11.

DISCUSSION

Cerebral myeloarchitecture develops across childhood and adolescence, and based on the current study, individual variability in the difference between intracortical and subjacent WM myelination likely has clinical relevance for a range of mental disorders, in particular anxiety and psychotic disorders. Based on T1-weighted brain scans from 1467 children and adolescents, we approximated myelination using the contrast in signal intensity between intracortical and subjacent WM across the brain. We found a global blurring of the GWC at higher ages, possibly in part reflecting protracted intracortical myelination compared with subjacent WM, with additional regional developmental patterns. Across individuals, regional GWC was associated with symptom burden, with significant associations to symptoms of anxiety and prodromal psychosis, and with general cognitive ability.

A broad range of psychopathology components were identified using a data-driven approach, and regional GWC was found to be associated with symptom levels of psychopathology within components reflecting several forms of anxiety and a component reflecting positive prodromal and advert psychosis. Higher levels of either anxiety or prodromal psychosis were associated with higher GWC in left lateral posterior and insula and cingulate cortices and lower contrast in sensorimotor cortices. Anxiety also showed positive associations in prefrontal and right lateral posterior cortices, while prodromal psychosis showed a positive association in the visual cortex and negative associations in medial temporal and superior frontal cortices. Although our original hypothesis was that increased symptom burden would be linked to regionally higher GWC, effects in both directions have been reported in prior studies (see below).

In addition to well-documented WM aberrations (19,59–61), there is accumulating evidence for abnormal intracortical myelination as a potential mechanism for brain network dysfunction in neurodevelopmental disorders and psychosis in particular (16). Myelin-related abnormalities in psychosis is indicated by genetic association studies (62), from postmortem studies (63,64), and from the notion that psychotropic treatments have effects on myelin and its plasticity and repair (65). Two previous studies have investigated GWC in adults with schizophrenia with similar methods. Kong *et al.* (38) reported decreased GWC in frontal and temporal regions, while Jørgensen *et al.* (37) in a larger study reported the opposite—in other words, increased GWC, yet in separate sensorimotor regions. Somewhat inconsistent with these studies, our results indicate that higher psychosis symptom levels in adolescents are associated with decreased GWC in pre- and postcentral cortices extending into superior frontal cortex and with increased GWC in left lateral posterior, insula and cingulate,

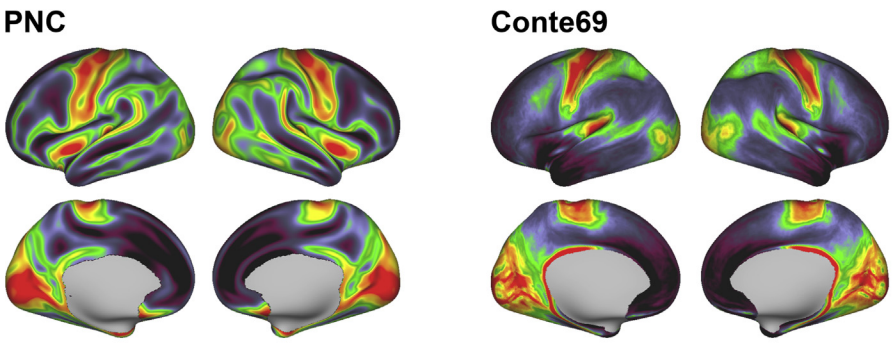

Figure 4. Mean gray/white matter contrast map vs. T1-T2 ratio map. The Philadelphia Neurodevelopmental Cohort (PNC) depicts the mean gray/white matter contrast surface maps of the current sample. Warm colors represent regions with lower gray/white matter contrast, while cold colors represent regions with higher gray/white matter contrast. Conte69 depicts a mean T1-T2 ratio map from young adults, based on 69 subjects (male = 38, female = 31, age = 9–45) (77). Warm colors are thought to represent regions with a high amount of intracortical myelin, while cold colors represent regions of low myelin content.

and visual cortices. The discrepancy could be due to analysis approach, sample age, or clinical characteristics. In addition to associations with prodromal psychosis, we also found associations with anxiety in partly overlapping regions.

We also investigated associations between general cognitive ability and GWC, hypothesizing that higher cognitive ability would be associated with lower GWC. The results indeed showed negative correlation in insula and cingulate, superior parietal, right lateral posterior, and visual cortices, but the results also show positive associations in medial temporal, pre- and postcentral, and orbitofrontal cortices. Interestingly, most of these regions overlapped with regions in which we found associations between GWC and psychopathology, with effects consistently in the opposite direction.

A few prior studies measuring either GWC or T1-T2 ratio have reported associations with cognitive functioning (25,26,66). For example, a study on youths reported that brain age gap computed using GWC was related to IQ (25). The effects in this study were driven by "decreased age" in sensorimotor regions and "increased age" in association cortices. Correspondingly, we found higher GWC in sensorimotor regions for participants with high cognitive functioning and lower GWC in large posterior regions, particularly in the right hemisphere. The observation that several of the GWC regions associated with gF overlapped with regions associated with psychopathology corresponds well with a separate study, also on the PNC sample, that reported that gF and mean psychopathology score share a genetic contribution (19).

In our follow-up analyses within Caucasians and African Americans/blacks separately, there were discrepancies in the association pattern between GWC and both psychopathology and gF. An exploration of possible genetic or environmental factors accounting for these discrepancies is beyond the scope of the current study. However, we note that neighborhood crime rate and parental education has previously been found to partially mediate the association between ethnicity and cognitive function in the PNC sample (67,68).

The global GWC component showed an age-related decrease across late childhood and adolescence. Although the microstructural underpinnings represent changes within both GM and WM, our results do fit well with prior studies employing cross-sectional MRI cortical intensity measures or postmortem histology of intracortical myelin. For instance, a study investigating cortical signal intensity reported a steady age-related decrease from childhood to adulthood (53), while a study employing T1-T2 ratio reported what was interpreted as an ongoing intracortical myelination process from 8 years of age extending well into adulthood (66). Correspondingly, a postmortem study reported that the maturation of human intracortical myelination extends past late adolescence (29).

Beyond the global age-related decrease in GWC, regional components showed both positive and negative age effects, which could in sum reflect regionally protracted and accelerated development, respectively. For instance, components encompassing primary sensorimotor or occipital regions showed negative associations with age. These regions have a high myelin content and mature early (23,24). In comparison, for example, the frontal lobe and temporal pole are known to continue intracortical myelination considerably longer (66,69), and the frontal lobe shows peak GM signal intensity later than the age range of the current sample (53). Components capturing these regions in the present study showed positive age associations, which, together with the global negative age effect, might indicate regionally protracted development.

Our GWC map showed high consistency with a mean T1-T2 ratio map provided by Human Connectome Project (24). The moderate correlation between the two maps could partly reflect differences in age range and scanner-related properties. Still, the strength of the correlations indicates that although the measures share variance, they also have specific, unique properties.

A limitation of the current study is that age-related differences in GWC cannot be specifically attributed to protracted intracortical myelination. Although our results converge with prior histological and MRI studies, the microstructural underpinnings of the measure are likely highly complex. Logically, GWC is a combination of both GM and WM, and loess visualizations indeed indicated similar age trajectories. Additionally, the biological interpretation of T1-T2 ratio as a proxy for intracortical myelin has come under scrutiny (70,71). Moreover, the intensity in T1-weighted images also reflects other biological properties, such as water content, iron, and dendrite density (39,72,73). Another study limitation is the potential for partial volume effects owing to sampling intensities close to the gray/white boundary. We chose this approach to include deeper, more myelinated layers of cortex. Partial volume effects could vary depending on cortical thickness, although vertexwise correlations between GWC and thickness were generally low, and adding thickness as a regressor had minor effects on vertexwise results. Lastly, the cross-sectional design, which is a nonoptimal indirect way of studying development (74), is a limitation to the current study.

The relevance of the current study is twofold. First, studies of individuals at risk for mental disorders have typically used genetic risk from family history or clinical risk measured as symptoms in help-seeking individuals (75). In contrast, the PNC sampling strategy taps into the continuum of psychopathology in youths. Thus, our findings may help define markers of neural dysfunction at both an earlier age and earlier stage of psychopathology development. This is critical for identifying biomarkers useful for early detection and eventually for prevention and early intervention (75,76). The finding that aberrations are already present in generally healthy youths with increased levels of anxiety and prodromal psychosis is an important addition to the literature. Second, we used data-driven approaches to identify a broad range of both psychopathology components and regional patterns in GWC, aiming to improve sensitivity and specificity, as associations between brain structure and psychopathology are typically small or moderate [see, e.g., (51)].

To conclude, the results of the current study showed that GWC globally decreases across late childhood and adolescence, likely partly reflecting the extended maturation of intracortical myelination as compared to subjacent WM. We additionally found regional developmental patterns possibly reflecting accelerated and protracted myelination. Across individuals, regional GWC was associated with symptom burden of anxiety and prodromal psychosis and general cognitive ability, supporting the clinical and neurocognitive relevance of this tissue contrast measure.

ACKNOWLEDGMENTS AND DISCLOSURES

This work was supported by the Department of Psychology, University of Oslo (to LBN and CKT), the Research Council of Norway (Grants Nos. 223273, 249795, 230345), the South-Eastern Norway Regional Health Authority (Grants No. 2014097, 2016083), and the European Commission's 7th Framework Programme (Grant No. 602450, IMAGEMEND). Support for the collection of The Philadelphia Neurodevelopment Cohort was provided by Grants No. RC2MH089983 to Raquel Gur and RC2MH089924 to Hakon Hakonarson. The participants were recruited through the Center for Applied Genomics at The Children's Hospital in Philadelphia. Data for this article was in part collected and shared by the Cambridge Centre for Ageing and Neuroscience. The U.K. Biotechnology and Biological Sciences Research Council (BB/H008217/1) provided Cambridge Centre for Ageing and Neuroscience funding, with support from the U.K. Medical Research Council and University of Cambridge, United Kingdom. Data were also in part provided by the WU-Minn HCP Consortium (Washington University, the University of Minnesota, and Oxford University Human Connectome Project Consortium) (Principal Investigators: David Van Essen and Kamil Ugurbil; Grant No. 1U54MH091657) funded by the 16 National Institutes of Health institutes and centers that support the National Institutes of Health Blueprint for Neuroscience Research, and by the McDonnell Center for Systems Neuroscience at Washington University.

Parts of the data in the present paper have previously been presented as a poster at the Society for Neuroscience 2017 annual meeting, and a preprint is published on bioRxiv.org.

The authors report no biomedical financial interests or potential conflicts of interest.

ARTICLE INFORMATION

From the Norwegian Centre for Mental Disorders Research (LBN, NTD, DA, TK, TM, JR, OAA, LTW), KG Jebsen Centre for Psychosis Research, Division of Mental Health and Addiction, Oslo University Hospital and Institute of Clinical Medicine, and Department of Psychology (LBN, JR, LTW, CKT), University of Oslo; and Department of Psychiatry (CKT), Diakonhjemmet Hospital, Oslo, Norway.

Address correspondence to Linn Bonaventure Norbom, M.D., University of Oslo, Department of Psychology, P.O. box 1094 Blindern, Oslo 0317, Norway. E-mail: l.c.b.norbom@psykologi.uio.no.

Received Apr 21, 2018; revised Sep 6, 2018; accepted Sep 24, 2018.

Supplementary material cited in this article is available online at https://doi.org/10.1016/j.biopsych.2018.09.027.

REFERENCES

1. Blakemore SJ, Mills KL (2014): Is adolescence a sensitive period for sociocultural processing? Annu Rev Psychol 65:187–207.
2. Crone EA, Dahl RE (2012): Understanding adolescence as a period of social-affective engagement and goal flexibility. Nat Rev Neurosci 13:636–650.
3. Lebel C, Beaulieu C (2011): Longitudinal development of human brain wiring continues from childhood into adulthood. J Neurosci 31:10937–10947.
4. Tamnes CK, Herting MM, Goddings AL, Meuwese R, Blakemore SJ, Dahl RE, *et al.* (2017): Development of the cerebral cortex across adolescence: a multisample study of inter-related longitudinal changes in cortical volume, surface area, and thickness. J Neurosci 37:3402–3412.
5. Herting MM, Johnson C, Mills KL, Vijayakumar N, Dennison M, Liu C, *et al.* (2018): Development of subcortical volumes across adolescence in males and females: A multisample study of longitudinal changes. Neuroimage 172:194–205.
6. Whitaker KJ, Vertes PE, Romero-Garcia R, Vasa F, Moutoussis M, Prabhu G, *et al.* (2016): Adolescence is associated with genomically patterned consolidation of the hubs of the human brain connectome. Proc Natl Acad Sci U S A 113:9105–9110.
7. Insel TR, Wang PS (2010): Rethinking mental illness. JAMA 303:1970–1971.
8. Insel TR (2010): Rethinking schizophrenia. Nature 468:187–193.
9. Murray RM, Bhavsar V, Tripoli G, Howes O (2017): 30 years on: How the neurodevelopmental hypothesis of schizophrenia morphed into the developmental risk factor model of psychosis. Schizophr Bull 43:1190–1196.
10. van Os J, Linscott RJ, Myin-Germeys I, Delespaul P, Krabbendam L (2009): A systematic review and meta-analysis of the psychosis continuum: Evidence for a psychosis proneness-persistence-impairment model of psychotic disorder. Psychol Med 39:179–195.
11. Lubke GH, Hudziak JJ, Derks EM, van Bijsterveldt TC, Boomsma DI (2009): Maternal ratings of attention problems in ADHD: Evidence for the existence of a continuum. J Am Acad Child Adolesc Psychiatry 48:1085–1093.
12. Kelleher I, Connor D, Clarke MC, Devlin N, Harley M, Cannon M (2012): Prevalence of psychotic symptoms in childhood and adolescence: A systematic review and meta-analysis of population-based studies. Psychol Med 42:1857–1863.
13. Ferdinand RF, van Lang ND, Ormel J, Verhulst FC (2006): No distinctions between different types of anxiety symptoms in pre-adolescents from the general population. J Anxiety Disord 20:207–221.
14. Fornito A, Bullmore ET (2015): Connectomics: A new paradigm for understanding brain disease. Eur Neuropsychopharmacol 25: 733–748.
15. Baumann N, Pham-Dinh D (2001): Biology of oligodendrocyte and myelin in the mammalian central nervous system. Physiol Rev 81: 871–927.
16. Bartzokis G (2012): Neuroglialpharmacology: myelination as a shared mechanism of action of psychotropic treatments. Neuropharmacology 62:2137–2153.
17. Krogsrud SK, Fjell AM, Tamnes CK, Grydeland H, Mork L, Due-Tonnessen P, *et al.* (2016): Changes in white matter microstructure in the developing brain: A longitudinal diffusion tensor imaging study of children from 4 to 11 years of age. Neuroimage 124:473–486.
18. Thomason ME, Thompson PM (2011): Diffusion imaging, white matter, and psychopathology. Annu Rev Clin Psychol 7:63–85.
19. Alnæs D, Kaufmann T, Doan N, Córdova-Palomera A, Wang Y, Bettella F, *et al.* (2018): Association of heritable cognitive ability and psychopathology with white matter properties in children and adolescents. JAMA Psychiatry 75:287–295.
20. Yakovlev PL, Lecours AR (1967): The myelogenetic cycles of regional maturation of the brain. In: Minkowski A , editor. Regional Development of the Brain Early in Life. Boston: Blackwell Scientific Publications Inc., 3–70
21. Sowell ER, Thompson PM, Leonard CM, Welcome SE, Kan E, Toga AW (2004): Longitudinal mapping of cortical thickness and brain growth in normal children. J Neurosci 24:8223–8231.
22. Shaw P, Kabani NJ, Lerch JP, Eckstrand K, Lenroot R, Gogtay N, *et al.* (2008): Neurodevelopmental trajectories of the human cerebral cortex. J Neurosci 28:3586.
23. Deoni SCL, Dean DC, Remer J, Dirks H, O'Muircheartaigh J (2015): Cortical maturation and myelination in healthy toddlers and young children. Neuroimage 115:147–161.
24. Glasser MF, Van Essen DC (2011): Mapping human cortical areas in vivo based on myelin content as revealed by T1- and T2-weighted MRI. J Neurosci 31:11597–11616.
25. Lewis JD, Evans AC, Tohka J (2018): T1 white/gray contrast as a predictor of chronological age, and an index of cognitive performance. Neuroimage 173:341–350.
26. Grydeland H, Westlye LT, Walhovd KB, Fjell AM (2016): Intracortical posterior cingulate myelin content relates to error processing: results from T1- and T2-weighted MRI myelin mapping and electrophysiology in healthy adults. Cereb Cortex 26:2402–2410.
27. Davis KL, Stewart DG, Friedman JI, Buchsbaum M, Harvey PD, Hof PR, *et al.* (2003): White matter changes in schizophrenia: evidence for myelin-related dysfunction. Arch Gen Psychiatry 60:443–456.
28. Lake EMR, Steffler EA, Rowley CD, Sehmbi M, Minuzzi L, Frey BN, *et al.* (2017): Altered intracortical myelin staining in the dorsolateral prefrontal cortex in severe mental illness. Eur Arch Psychiatry Clin Neurosci 267:369–376.
29. Miller DJ, Duka T, Stimpson CD, Schapiro SJ, Baze WB, McArthur MJ, *et al.* (2012): Prolonged myelination in human neocortical evolution. Proc Natl Acad Sci U S A 109:16480–16485.

30. Paus T, Keshavan M, Giedd JN (2008): Why do many psychiatric disorders emerge during adolescence? Nat Rev Neurosci 9:947–957.
31. Koenig SH, Brown RD 3rd, Spiller M, Lundbom N (1990): Relaxometry of brain: why white matter appears bright in MRI. Magn Reson Med 14:482–495.
32. Koenig SH (1991): Cholesterol of myelin is the determinant of gray-white contrast in MRI of brain. Magn Reson Med 20:285–291.
33. Eickhoff S, Walters NB, Schleicher A, Kril J, Egan GF, Zilles K, *et al.* (2005): High-resolution MRI reflects myeloarchitecture and cytoarchitecture of human cerebral cortex. Hum Brain Mapp 24:206–215.
34. Stuber C, Morawski M, Schafer A, Labadie C, Wahnert M, Leuze C, *et al.* (2014): Myelin and iron concentration in the human brain: A quantitative study of MRI contrast. Neuroimage 93:95–106.
35. Panizzon MS, Fennema-Notestine C, Kubarych TS, Chen CH, Eyler LT, Fischl B, *et al.* (2012): Genetic and environmental influences of white and gray matter signal contrast: A new phenotype for imaging genetics? Neuroimage 60:1686–1695.
36. Vidal-Pineiro D, Walhovd KB, Storsve AB, Grydeland H, Rohani DA, Fjell AM (2016): Accelerated longitudinal gray/white matter contrast decline in aging in lightly myelinated cortical regions. Hum Brain Mapp 37:3669–3684.
37. Jørgensen KN, Nerland S, Norbom LB, Doan NT, Nesvag R, Morch-Johnsen L, *et al.* (2016): Increased MRI-based cortical grey/white-matter contrast in sensory and motor regions in schizophrenia and bipolar disorder. Psychol Med 46:1971–1985.
38. Kong L, Herold CJ, Zollner F, Salat DH, Lasser MM, Schmid LA, *et al.* (2015): Comparison of grey matter volume and thickness for analysing cortical changes in chronic schizophrenia: A matter of surface area, grey/white matter intensity contrast, and curvature. Psychiatry Res 231:176–183.
39. Bansal R, Hao X, Liu F, Xu D, Liu J, Peterson BS (2013): The effects of changing water content, relaxation times, and tissue contrast on tissue segmentation and measures of cortical anatomy in MR images. Magn Reson Imaging 31:1709–1730.
40. Satterthwaite TD, Elliott MA, Ruparel K, Loughead J, Prabhakaran K, Calkins ME, *et al.* (2014): Neuroimaging of the Philadelphia Neurodevelopmental Cohort. Neuroimage 86:544–553.
41. Satterthwaite TD, Connolly JJ, Ruparel K, Calkins ME, Jackson C, Elliott MA, *et al.* (2016): The Philadelphia Neurodevelopmental Cohort: A publicly available resource for the study of normal and abnormal brain development in youth. Neuroimage 124:1115–1119.
42. Calkins ME, Merikangas KR, Moore TM, Burstein M, Behr MA, Satterthwaite TD, *et al.* (2015): The Philadelphia Neurodevelopmental Cohort: Constructing a deep phenotyping collaborative. J Child Psychol Psychiatry 56:1356–1369.
43. Gur RC, Richard J, Calkins ME, Chiavacci R, Hansen JA, Bilker WB, *et al.* (2012): Age group and sex differences in performance on a computerized neurocognitive battery in children age 8–21. Neuropsychology 26:251–265.
44. Merikangas KR, Calkins ME, Burstein M, He J-P, Chiavacci R, Lateef T, *et al.* (2015): Comorbidity of physical and mental disorders in the Neurodevelopmental Genomics Cohort Study. Pediatrics 135:e927–e938.
45. Himberg J, Hyvarinen A, Esposito F (2004): Validating the independent components of neuroimaging time series via clustering and visualization. Neuroimage 22:1214–1222.
46. Fischl B (2012). FreeSurfer. Neuroimage 62:774–781.
47. Fischl B, Salat DH, Busa E, Albert M, Dieterich M, Haselgrove C, *et al.* (2002): Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. Neuron 33: 341–355.
48. Dale AM, Fischl B, Sereno MI (1999): Cortical surface-based analysis. I. Segmentation and surface reconstruction. Neuroimage 9:179–194.
49. Fischl B, Sereno MI, Dale AM (1999): Cortical surface-based analysis. II: Inflation, flattening, and a surface-based coordinate system. Neuroimage 9:195–207.
50. Hubert M, Engelen S (2004): Robust PCA and classification in biosciences. Bioinformatics 20:1728–1736.
51. Moberget T, Doan NT, Alnaes D, Kaufmann T, Cordova-Palomera A, Lagerberg TV, *et al.* (2017): Cerebellar volume and cerebellocerebral structural covariance in schizophrenia: A multisite mega-analysis of 983 patients and 1349 healthy controls. Mol Psychiatry 23:1512–1520.
52. Rosen AFG, Roalf DR, Ruparel K, Blake J, Seelaus K, Villa LP, *et al.* (2018): Quantitative assessment of structural image quality. Neuroimage 169:407–418.
53. Westlye LT, Walhovd KB, Dale AM, Bjørnerud A, Due-Tønnessen P, Engvig A, *et al.* (2010): Differentiating maturational and aging-related changes of the cerebral cortex by use of thickness and signal intensity. Neuroimage 52:172–185.
54. Westlye LT, Walhovd KB, Dale AM, Espeseth T, Reinvang I, Raz N, *et al.* (2009): Increased sensitivity to effects of normal aging and Alzheimer's disease on cortical thickness by adjustment for local variability in gray/white contrast: A multi-sample MRI study. Neuroimage 47:1545–1557.
55. Genovese CR, Lazar NA, Nichols T (2002): Thresholding of statistical maps in functional neuroimaging using the false discovery rate. Neuroimage 15:870–878.
56. Wickham H (2009): ggplot2: Elegant Graphics for Data Analysis. New York: Springer-Verlag.
57. Winkler AM, Ridgway GR, Webster MA, Smith SM, Nichols TE (2014): Permutation inference for the general linear model. Neuroimage 92:381–397.
58. Smith SM, Nichols TE (2009): Threshold-free cluster enhancement: addressing problems of smoothing, threshold dependence and localisation in cluster inference. Neuroimage 44:83–98.
59. Canu E, Agosta F, Filippi M (2015): A selective review of structural connectivity abnormalities of schizophrenic patients at different stages of the disease. Schizophr Res 161:19–28.
60. O'Hanlon E, Leemans A, Kelleher I, Clarke MC, Roddy S, Coughlan H, *et al.* (2015): White matter differences among adolescents reporting psychotic experiences: A population-based diffusion magnetic resonance imaging study. JAMA Psychiatry 72:668–677.
61. Bora E, Fornito A, Radua J, Walterfang M, Seal M, Wood SJ, *et al.* (2011): Neuroanatomical abnormalities in schizophrenia: A multimodal voxelwise meta-analysis and meta-regression analysis. Schizophr Res 127:46–57.
62. Steen VM, Skrede S, Polushina T, López M, Andreassen OA, Fernø J, *et al.* (2017): Genetic evidence for a role of the SREBP transcription system and lipid biosynthesis in schizophrenia and antipsychotic treatment. Eur Neuropsychopharmacol 27:589–598.
63. Tkachev D, Mimmack ML, Ryan MM, Wayland M, Freeman T, Jones PB, *et al.* (2003): Oligodendrocyte dysfunction in schizophrenia and bipolar disorder. Lancet 362:798–805.
64. Uranova NA, Vikhreva OV, Rachmanova VI, Orlovskaya DD (2011): Ultrastructural alterations of myelinated fibers and oligodendrocytes in the prefrontal cortex in schizophrenia: a postmortem morphometric study. Schizophr Res Treatment 2011:325789.
65. Bartzokis G (2011): Neuroglialpharmacology: white matter pathophysiologies and psychiatric treatments. Front Biosci 16:2695–2733.
66. Grydeland H, Walhovd KB, Tamnes CK, Westlye LT, Fjell AM (2013): Intracortical myelin links with performance variability across the human lifespan: Results from T1- and T2-weighted MRI myelin mapping and diffusion tensor imaging. J Neurosci 33:18618–18630.
67. Moore TM, Martin IK, Gur OM, Jackson CT, Scott JC, Calkins ME, *et al.* (2016): Characterizing social environment's association with neurocognition using census and crime data linked to the Philadelphia Neurodevelopmental Cohort. Psychol Med 46:599–610.
68. Barzilay R, Calkins ME, Moore TM, Wolf DH, Satterthwaite TD, Cobb Scott J, *et al.* (2019): Association between traumatic stress load, psychopathology, and cognition in the Philadelphia Neurodevelopmental Cohort. Psychol Med 49:325–334.
69. Bartzokis G (2004): Age-related myelin breakdown: a developmental model of cognitive decline and Alzheimer's disease. Neurobiol Aging 25:5–18.

70. Ritchie J, Pantazatos SP, French L (2018): Transcriptomic characterization of MRI contrast with focus on the T1-w/T2-w ratio in the cerebral cortex. Neuroimage 174:504–517.
71. Hagiwara A, Hori M, Kamagata K, Warntjes M, Matsuyoshi D, Nakazawa M, *et al.* (2018): Myelin measurement: comparison between simultaneous tissue relaxometry, magnetization transfer saturation index, and T1w/T2w ratio methods. Sci Rep 8:10554.
72. Righart R, Biberacher V, Jonkman LE, Klaver R, Schmidt P, Buck D, *et al.* (2017): Cortical pathology in multiple sclerosis detected by the T1/T2-weighted ratio from routine magnetic resonance imaging. Ann Neurol 82:519–529.
73. Bulk M, Abdelmoula WM, Nabuurs RJA, van der Graaf LM, Mulders CWH, Mulder AA, *et al.* (2018): Postmortem MRI and histology demonstrate differential iron accumulation and cortical myelin organization in early- and late-onset Alzheimer's disease. Neurobiol Aging 62:231–242.
74. Kraemer HC, Yesavage JA, Taylor JL, Kupfer D (2000): How can we learn about developmental processes from cross-sectional studies, or can we? Am J Psychiatry 157:163–171.
75. Satterthwaite TD, Wolf DH, Calkins ME, Vandekar SN, Erus G, Ruparel K, *et al.* (2016): Structural brain abnormalities in youth with psychosis spectrum symptoms. JAMA Psychiatry 73:515–524.
76. Insel TR (2009): Translating scientific opportunity into public health impact: A strategic plan for research on mental illness. Arch Gen Psychiatry 66:128–133.
77. Van Essen DC, Glasser MF, Dierker DL, Harwell J, Coalson T (2012): Parcellations and hemispheric asymmetries of human cerebral cortex analyzed on surface-based atlases. Cereb Cortex 22:2241–2262.